REMARKS

I. Status of Claims

Claims 1- 4, 6-43, 45,47-51 are cancelled.

Claim 5 is amended.

Claims 5, 44 and 46 are being prosecuted.

II. A Prima Facie Case of Obviousness is Not Established

Claims 5, 44, 47 and 48 were rejected under 35 USC 103(a) over **Momany** (EP 00180072) in view of **Barany et al.** (US patent 5235028).

Claim 5 was previously amended to include "68%" "of the D-peptides comprise at least three aromatic amino acid residues,---". Support was provided in the record for 68%. Claim 46 was amended to add "---and D-histidine." Claims 48 – 51 were new claims. The rejection of claims 5, 44 and 46 as being anticipated by **Momany** (EP 00180072) was withdrawn by the Examiner.

Claim 5 is amended herein replacing "comprising" with "consisting of" to limit the claim scope. Claims 45, 47-51 are cancelled. Therefore, some arguments are moot, but are presented for the record.

The Examiner responded to applicant's argument that **Momany** does not show certain features of the claimed invention, specifically that the library claimed contains all possible combinations of all the particular amino acids used to construct the library, in contrast to **Momany** who only has made many peptides based upon prior knowledge of some of the data concerning amino acids important in the growth hormone (GH) receptor interaction and does not teach a specific combinatorial library as in amended claim 5. The Examiner maintained that the rejected claims do not recite that the library contains all possible combinations of all the amino acids making up the library.

Glycine and D-alanine are specific in claim 5 as the remaining amino acid residues, to compose the combinatorial library. Three aromatic amino acids are specific in dependent claim 46. A combinatorial library is defined as one containing all possible combinations of the elements of the library so that characteristics need not be expressed in the claims. The specification clearly states and describes the construct of the libraries:

1. page 4, para 0016: " - - - a pentapeptide library enriched in aromatic D-amino acids was constructed in a split synthesis method using four D-amino acids, alanine, phenylalanine, tyrosine and tryptophan, and glycine."
2. and in para 18: "The split synthesis method yields beads each of which comprise multiple copies of a single D-peptide sequence.

With five amino acids, the number of different pentapeptide sequences in the resulting library is 5 to the fifth power or 3125 and on page 13, para 0049, the details of the synthesis of the library are described.

"Because five amino acids were used at each of five amino acid adding steps, the resulting bead library contains 3125 pentapeptide sequences."

Those of skill in the art of peptide libraries, or combinatorial libraries of any other compositions, would realize that all possible combinations of peptides necessarily result. Stating in the claims that peptide libraries composed of the elements in the specification, would contain all possible combinations of the amino acids, would be redundant and certainly not necessary to support the validity of the pending claims.

With regard to what constitutes the libraries, the amino acid components, and the resulting peptide sequences obtained in constructing the libraries, there is no limitation needed.

The examiner "agrees that **Momany**, in family III, teaches a library of peptides wherein 50% contain 3 aromatic acids of D-Tyr, D-Trp and D-Phe." Applicant previously amended claim 5 to be limited to at least 68% of the D-peptide having at least 3 aromatic amino acid residues.

With regard to solubility, the Examiner states (page 4, paragraphs 1, 2 and 3) that some of the peptides of **Momany** are constructed with 3 aromatic D-aromatic residues and additional amino acids so as to enhance solubility. The Examiner states: "- - - the aromatic tripeptide *sequences* (i.e., Y3-Z3-E3) of **Momany** are taken as conjugated to enhance solubility to another peptide, (i.e. G3-J3)." The Examiner does not mean to "another peptide" but rather the additional amino acids of the particular peptides synthesized by **Momany**. Further, the Examiner points out that those additional amino acids, additional to the 3 aromatic residues, can be such as to enhance solubility in water based solutions or in organic solvents.

As the examiner admits, the only groups of **Momany** containing 3 D-aromatic residues are groups III and XIII, and all the peptides synthesized by **Momany**, only a very small percent had 3 D-

aromatic residues. The inventor analyzed the 188 peptide sequences in **Momany** with regard to amino acid residues in addition to the aromatic amino acids:

Only 1 sequence that contained the 3 D-aromatic residues had a lysine residue as well.

53 of the sequences (28.2%) had no additional non-aromatic residues.

37 of the sequences (19.7%) had an arginine or lysine residue.

57 of the sequences (30.3%) had one of the J3 residues (proline, serine, threonine, alanine, etc.). Only 4 of the 57 J3 residues (7.0%, and 0.21% of the total sequences) had amino acids that would enhance solubility in polar solvents.

11 of the sequences (5.85%) had 2 additional residues of the J3 group, one of which was more hydrophilic and the second being more hydrophobic.

Based on the above range of percentages of additional (to the aromatic residues) hydrophilic and hydrophobic amino acids, one of skill in the art would not conclude that **Momany** teaches adding amino acids to enhance solubility. Nowhere in **Momany** does he even mention solubility issues and certainly not adding particular amino acids to the peptides for solubility purposes, whether in polar or non-polar solvents.

In the pending specification peptides are specified as soluble in water based solvents and environments. "--- the D-peptides - - - were - - - synthesized to include three D-lysine residues at the C-terminal ends of the D-peptides to enhance solubility," (page 9, para 0037) and the experimental examples of pages 27 (dissociation constants) and 28 and 29, (Prolongation of survival - - -) use certain peptides containing 3 or 4 D-aromatic residues and 3 D-Lys residues.

Momany would not lead to the conclusion to add D-Lys, or other residues to enhance solubility in water based solvents. Rather the claimed aromatic rich peptide sequences would likely not be soluble in water based solvents. Because the inventors intended to use the aromatic peptides in water based solvents and in *in vivo* conditions, it should be evident to those skilled in the art that some modification of the aromatic peptides would need to be made to effect solubility in polar solvents.

In review of the data of Table II of **Momany**, only 1 peptide (of 36) was tested that contained the 3 D-aromatic residues as well as a L-Lys residue for *in vitro* growth hormone release. Also, for other peptides tested, only 1 out of 4 (of the 36 peptides so tested) contained either D- or L-configuration Lys residues. Based on those data, one skilled in the art, would not conclude that any addition (Lys or Arg, or other non-polar residue) is an important teaching. **Momany** neither

suggested nor stated explicitly, that addition of certain amino acid residues was of importance to a solubility issue. **Momany** makes no comment on the solubility of any of the peptides, or peptide groups specified in the claims, as to solubility issues.

Amended claim 5 relates that the peptides of the present application are all soluable regardless of their structure, because they are linked to a support. According to the examiner, **Barany**, in using polyoxyethylene (polyethylene glycol, PEG) chains substituted onto polystyrene (PS) for the use of peptide syntheses, would make it obvious that the PEG chains would increase, or allow, hydrophobic peptide sequences to be soluble in non-polar solvents. Thus, one could extend this thinking to include that addition of any the more polar amino acid residues in a peptide sequence of several non-polar residues (e.g., the aromatic amino acids), would also increase the polar solvent solubility of the aromatic rich peptides of our specification. However, **Barany did** conclude follows:

In **Barany** et al. (USPTO 5,235,028), the advantages of PEG substituted PS for the synthesis of peptides includes:

1. "- - PEG-PS graft supports made by the methods of this invention are particularly useful. PEG-PS supports made using the present PEG derivatives have several characteristics for solid-phase applications: they swell in a variety of solvents, are stable under the conditions used in most solid-phase synthesis, and behave well in both batch and column reactors used for solid-phase applications, in particular, solid-phase peptide synthesis." Page 7 of **Barany** et al. Second paragraph.
2. "The -- - (PEG-PS) graft supports showed reproducible advantage over PS supports - - - . The PEG-PS supports - - - allowed peptide synthesis using acetonitrile - - -." Page 8, top of the page.
3. Page 8, first paragraph: "The PEG-PS material proved highly suitable both for flow-through synthesis and batch operation." And, "The peptide was produced in higher purity on this new PEG-PS - - -."
4. Page 8, second paragraph: "The general usefulness of the PEG-PS graft support was demonstrated by the synthesis of a number of large - - - complex peptide sequences, such as - - ." And: "The improvements in synthetic efficiency which resulted from use of the present PEG-PS linkers appear to originate from one or more of the following: (i) a spacer arm effect removing the reaction sites from the velocity of the

> polymer backbone; (ii) a general environmental effect which modifies the hydrophobic nature of the resin with a concomitantly favorable influence on reaction rates; and (iii) a specific effect conformationally difficult couplings due to increased secondary structure (hydrogen bond formation)."

Barany et al. make no inference or claim, or advantage, of the PEG-PS support in terms of the solubility issue.

The present specification, (page 5, paragraph 0019), teaches "Because the polyoxyethlene (PEG) arms of the TentaGel beads are water soluble, the conformations of the D-peptide are determined primarily by thermodynamics and by their primary sequence." Conformations of the aromatic rich peptides, as attached to the PEG-PS, would be similar and, indeed most likely, identical to their conformations as free peptides, an important consideration in interpreting and finding peptides of usefulness in biologic systems in consideration their binding to various proteins of interest.

TentaGel beads (PEG-PS) with the aromatic rich peptides attached were used because the PEG separates (by about 150 angstroms for extended conformation of the PEG) the peptide from being near the PS and thus reduces any possible adsorption of peptides to the PS. Also, the PEG portion can effectively block a protein from finding its way to the PS and non-specifically binding; and important consideration in screening assays using the peptides on the TentaGel beads.

The Examiner next argues against "- - - are not applicable to finding binding partners for any protein of interest." (page 4, paragraph 4.) The Examiner replies (page 4, paragraph 5) that "- - - the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." And "If the prior art structure is capable of performing the intended use, then it meets the claim." Furthermore (page 5, first and second paragraphs) the Examiner points out that in claim 5 68% of peptides will contain 3 or more aromatic D-configuration amino acids (and claim 48 is drawn to 100%), whereas **Momany** has examples of peptide groups containing 50% of D-aromatic amino acids. The Examiner submits in accordance with MPEP 2144.05 II A that, generally, "- - - differences in concentration - - - will not support patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration - - - is critical."

Momany's disclosed range is so broad as to encompass a very large number of possible distinct compositions and this might present a situation analogous to the obviousness of a species

when the prior art broadly discloses a genus. *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005).

"The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. . . . In such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). There are really no "prior art ranges" because no publication cited **teaches** the library of claim 5 as such, to those of skill in the art.

A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result- effective variable.). There is no recognition in the prior art of the libraries of claim 5, nor their value. The present application presents advantages of the libraries.

Momany, and for that matter **Dooley** et al., are focused on single protein targets in their quest to find peptides that may be used to elicit a growth hormone release (**Momany**) or to interact with an opioid receptor. A uniqueness of the present invention is the realization and findings that libraries of aromatic rich peptides can be used to screen for particular aromatic rich peptides that will bind with high affinities and specificities to any protein of interest. "Any" does not mean that every protein will have a binding ligand in the aromatic rich peptides libraries of the invention; it rather means that the invention can identify an aromatic rich peptide(s) that binds with high affinity and specificity to any protein of interest. None of the literature data, and none of the data and the claims in patents, lead to the generalization that libraries, which will be intrinsically enriched in aromatic residues, could be used to identify particular aromatic rich peptides that would exhibit high affinities and specificities to proteins of interest. In contrast, the specification (pages 24 and 25, paragraphs 0074, Table 6, and paragraph 0080, Table 7) demonstrate that aromatic rich peptides were identified to 14 different, and quite different proteins in terms of primary sequences and of function. This is not a matter of "- - - finding optimal or workable ranges by routine experimentation." (page 5, paragraph 3 of the Examiner; *In re Aller* - - -), but rather use of a quite different approach than

Momany, or any other literature or patent the Examiner has cited. The approach of **Dooley** et al. is very different.

Momany starts with the hypothesis that the growth hormone interacts with its receptor in a manner similar to other Met-enkefalins and that one or two aromatic amino acids may be important in those binding interactions. **Dooley** at al. start with the hypothesis that a library of all possible amino acid combinations of a hexapeptide, using an interactive experimental procedure of making mixtures of peptides from the total library, can be used to find binding partners to an opiod receptor. In both cases they find peptides that have more than one aromatic amino acid, and for **Dooley** et al., they also find that D-configuration peptide libraries can result in finding an aromatic rich hexapeptide with affinity about a hundred-fold less that an aromatic rich peptide of L-configuration amino acids.

In contrast, the basis of the present invention is:

1. A relatively hydrophobic ligand can enter into a relatively hydrophilic, or relatively hydrophobic, protein binding site as long as the ligand is of a size and 3D geometry to accommodate within that protein binding site. The affinity of any particular hydrophobic ligand in the binding site is proportional to the number and strengths of the non-covalent binding interactions between the ligand and the residues of the protein making up that binding site.
2. Many binding sites of proteins contain hydrophobic residues in the binding sites, even those that bind more hydrophilic ligands like carbohydrate ligands, and that these hydrophobic binding site residues tend to be aromatic R groups of amino acids in the protein binding site. In some of the cases, homologous proteins, such as the serotypes of the botulinum toxin proteins and the influenza serotype hemagglutinin proteins, contain invariant aromatic amino acids in their binding sites, which are not only invariant in terms of position in amino acid sequence, but also in their geometry in the binding sites.
3. If an aromatic rich peptide has the proper geometry to access a protein binding site containing one or more aromatic R groups projecting into such site, the aromatic – aromatic bonding interactions will have an entropic component that can be predicted to result in a binding affinity which may be greater, or much greater, than that binding

site for its natural ligand because of an expected entropic contribution to the binding affinity.

4. The chemical nature of the aromatic amino acids and their intrinsic abilities to make non-covalent bonding interactions with other R groups of amino acids.

The two most hydrophobic R groups of the amino acids are tryptophan and phenylalanine; tyrosine, because of the hydroxyl group (which is in the para ring position of phenylalanine) yields sufficient hydrophilic character that tyrosine is in the intermediate position of hydrophobicity of the amino acids.

The consequences of the abilities of these aromatic amino acids is that R groups of tryptophan, phenylalanine and tyrosine can non-covalently bond to both the more hydrophobic R groups of the amino acids as well as the more hydrophilic R groups of amino acids. This is a property of the aromatic R groups which is not generally realized by those skilled in the art of peptide interactions or of ligand interactions with protein binding sites.

The reason for the unique properties of the aromatic groups is that the aromatic ring structures result in an electron density of phenylalanine, tyrosine and phenylalanine of the pi electrons which are delocalized around the ring structures. This imparts a delta negative charge on each side of the ring structures. There is a resulting delta positive charge around the relatively planar ring structures which encompasses the positions of the hydrogen atoms. For this reason, aromatic – aromatic ring R group non-covalent bonding interactions position the rings in a perpendicular orientation. This preferred conformational arrangement of the R groups of aromatic amino acid R groups occurs in 90% of all aromatic – aromatic ring non-covalent bonding interactions.

Because of the delta negative charge on either face of the aromatic faces of phenylalanine, tyrosine and tryptophan amino acids in proteins, amino acids whose R groups are a net positive charge, e.g., arginine or lysine, will non-covalently bond to the faces of the aromatic rings; and amino acids of a more negative charge can non-covalently bond to the periphery of the aromatic rings which carry a delta positive charge.

However, the R group aromatic rings still display a net hydrophobic character such that hydrophobic amino acid R groups, such as found on the amino acid leucine or valine, can form van der Waals non-covalent bonding interactions with the aromatic ring structures.

Thus, the aromatic R groups of phenylalanine, tyrosine and tryptophan are rather equivalent to an amphoteric solvent, such as dimethylsulfoxide (DMSO) or dimethylformamide (DMF) in promoting solubility of both hydrophilic and hydrophobic molecules.

This fact is not realized or reported by those skilled in the art of biochemistry and even peptide chemistry and ligand - protein interactions.

The consequences of these 4 points are that one may expect that peptides enriched in the aromatic amino acids may find binding partners to many protein binding sites, especially those that contain one or more aromatic R groups in those binding sites, and regardless of the other non-aromatic R groups making up the binding sites. Furthermore, one may expect that aromatic rich peptides, or other aromatic rich compounds, could bind to proteins of interest and effect a physiologic effect of medical importance.

Claims 5, 44, 46, 47, 49, and 50 are rejected under 35 USC §103(a) over **Dooley** and **Barany**.

The Examiner states that **Dooley** et al. teach in claim 2 a hexapeptide having the structure (all D-configuration amino acids) Ac-r-f-w-w-g-x where x may be any of the common amino acids, and that **Dooley** et al. synthesize an intermediate of f-w-w-g- x-resin as an intermediate; thus the peptide intermediate comprises 3 D-aromatic amino acids meeting the enrichment claims of 5 and 49. Also, the same resin can be thought of as a tetrapeptide, reading on claim 49 constructed to enhance solubility through a x residue which may be k or r amino acids reading on claims 5, 44, 46 and 49.

Then, one of ordinary skill in the art (page 10, para 3), (recognizing the favorable solubility factor of k or r residues), would have, in view of **Barany** et al., used PEG attached to the PS support (bead) to effect an enhanced solubility of our aromatic rich D-peptides. Thus, the Examiner continues, the tetrapeptide on the PEG-PS resin reads on the library set forth in claim 50 including the sequences of f-w-w-g-g—PEG-PS and f-w-w-g-a-PEG-PS.

The Examiner continues that "- - -one of ordinary skill in the art would have - - :" 1. "--_been motivated to make peptides of **Dooley** et al. using PEG-PS of **Barany** et al. because PEG-PS provides better peptides, - - " and 2. there was "- - -a reasonable expectation of success in applying **Barany** et al. toward synthesis of the peptides according to **Dooley** et al. because both are concerned with preparing peptides - - - (peptides of **Dooley** lie within scope of **Barany** et al.)- - ."

In summary: **Dooley** et al. prepared a library of 52,128,400 hexapeptide sequences (with an acetyl group at the N-terminal ends and NH2 groups at the C-terminal ends (both of these functional

groups reduce the solubility of any peptide in comparison to the N- and C-terminal ends being not blocked by those functional groups.) The library consists of 400 mixtures of hexapeptides where the first 2 amino acid residues are known (20 x 20 = 400) and the other 4 positions are mixtures of all other amino acid residues except cys (so 19 amino acids) – 20 x 20 x 19 x 19 x 19 x 19 = the 52,128,400 number of hexapeptide sequences. They tested all 400 mixtures in an assay of their mixtures as effective in binding to mu opioid receptor. Based on those results they see which first 2 amino acids are the most active in the mixtures of the other 4 amino acids. They then take the chosen 2 amino acid peptide mixture and prepare another mixture wherein the third amino acid is varied for all 19 amino acids (again all natural amino acids except cys) and again pick out the3 most active amino acid at the third position. Then they do the same type of prep of mixtures at the fourth position. This they call an iterative procedure. Through this procedure they picked out the 4 amino acid hexapeptide sequences as discussed in the patent of **Dooley** (there were 4 different screening procedures, 3 with the D-configuration amino acids and 1 with the L-configuration amino acids.

The library of **Dooley** et al. contain only a very small percentage of peptides that would consist of 3 or more aromatic residues (as compared to the libraries of claim 5). Thus the presently claimed libraries were quite different.

Dooley et al. cite the relevant document of Goldstein et al. (US patent 4,396,606) which describes the dynorphin peptide that binds to the opioid receptors. The dynorphin has one part of its sequence as containing 2 aromatic amino acids and 4 hydrophobic residues (2 of which are aromatic residues), in addition to 2 arginine and 2 lysine residues (dynorphin A), and dynorphin B subcomponent contains a similar mix of aromatic and basic amino acids (i.e., arginine and lysine). Goldstein, in his publications, describes the isolation and amino acid sequences of dynorphin and its subcomponents.

Considering the specific examples of sequences discerned by **Dooley** et al. to a specific target molecule (the receptor of the mu opioid receptor), and the amino acid composition and sequences of the dynorphbin peptides, there is no expectation that one with ordinary skill in the art would make a conclusion that aromatic rich peptides may generally find binding partners to a number of proteins of diverse sequences and 3D structures (and their binding sites to ligands of diverse chemical structure and properties).

Dooley et al. had apparently favored an arginine residue in their peptides, as well as a lysine residue, based on the fact that the dynorphin A and B sequences required such residues.

Furthermore, the conformations of the aromatic peptides would be independent of the PEG linker region between the resin (PS).

The experimental approaches of both **Momany** and **Dooley** et al. were directed to particular protein targets and the examiner has not provided evidence that one of skill in the art would be taught from their results that aromatic rich peptides are ligands for potentially many protein binding sites.

III. Claims Satisfy 35 U.S.C. 112

Claims 47-49 and 51 are cancelled making their rejection moot.

Claim 50 was not rejected.

Claims 5, 44 and 46 only include "**at least** 68%."

The 68% figure in claim 5, and the 100%, 73% and 80% figures of claims 48, 49 and 51, respectively (now cancelled), are intrinsic to the construct of the libraries. In the split synthesis method, and using the particular amino acid residues specified, the percents cannot be anything other than the percents stated in those claims. Thus, what percents of each library, tri- to hepta-peptide in length, will contain 3 or more aromatic D-amino acid residues. An analogy would be the following: "If I were to say that I will give $1,000 in ten dollar bills, I do not have to state to you that I will give you 100 $10 dollar bills; the 100 number is intrinsic to what I stated I would give you and I need not state that number." The 68% figure applies to all peptides having from 3-7 amino acids because it is a minimum.

IV. Other Issues

Applicant thanks the examiner for withdrawing previous rejections, and requested allowance of the pending claims. Please charge any deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (45240-105719).

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